MTF Formulary Management for Chronic Myelogenous Leukemia (CML)

Defense Health Agency Pharmacy Operations Division

Bottom Line

- **All drugs in the CML Subclass are on the Uniform Formulary.**
- **In the frontline setting for CML, imatinib (Gleevec) and the second-generation agents, dasatinib (Sprycel) and nilotinib (Tasigna), are recommended.**
- **No agent was selected for Extended Core Formulary (ECF) status.**

Uniform Formulary Decision: The Director, DHA, approved the recommendations from the August 2015 DoD P&T Committee meeting on October 30, 2015.

Uniform Formulary (UF) Agents		Nonformulary (NF) Agents
	MTFs <u>may</u> have on formulary	**MTFs <u>must not</u> have on formulary**
None	• imatinib (Gleevec) • dasatinib (Sprycel) • nilotinib (Tasigna) • bosutinib (Bosulif) • ponatinib (Iclusig)	None

Clinical Summary

Treatment of CML Chronic Phase

- Imatinib (Gleevec), nilotinib (Tasigna), and dasatinib (Sprycel) are the three tyrosine kinase inhibitors (TKIs) approved in the United States for first-line therapy of CML; they have documented survival benefits.
- Head-to-head trials between imatinib and the second-generation TKIs found that dasatinib and nilotinib yield superior and more rapid hematologic, cytogenetic, and molecular responses in patients with chronic phase CML. However, to date, there are no statistically significant differences in overall survival between imatinib and the second-generation TKIs.
- Imatinib is associated with improved survival, with results from the International Randomized Study of Interferon versus STI571 trial (IRIS) showing overall survival of 85% at 8-year follow-up. The IRIS study and long-term follow-up data showed that imatinib induces highly durable responses with a low relapse rate in a large portion of chronic phase CML patients.
- In the DASISION trial, 76% of dasatinib-treated patients achieved major molecular response (MMR) by 5 years, compared with 64% of imatinib-treated patients. While there was a trend in favor of dasatinib, progression to accelerated or blast phase CML was not statistically different between the two groups (2% versus 3.5%).
- In the ENESTnd trial, 77% of nilotinib patients achieved MMR by 5 years, compared with 60% of imatinib patients. Additionally, the ENESTnd trial demonstrated a significant reduction in progression to accelerated or blast phase CML for patients who received nilotinib.
- Imatinib advantages include pending generic availability, a well-known safety profile, and additional FDA-approved indications other than CML. The second generation TKIs dasatinib and nilotinib are preferred for use in moderate- to high-risk patients.
- In patients with imatinib resistance or intolerance, dasatinib, nilotinib, or bosutinib (Bosulif) can be used. Bosutinib and ponatinib (Iclusig) are considered second-line agents with specific indications for use in certain mutations or use only after failure of first-line therapies.

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Safety

- The toxicities of the CML drugs differ and are taken into consideration when selecting treatments for individual patients.
- Major grade 3/4 adverse effects typically occur during the first phase of treatment and are manageable. Anemia, thrombocytopenia, and neutropenia are issues common to all the CML drugs.
- Imatinib adverse events include fatigue, myalgias, and fluid retention. Dasatinib has been associated with pleural effusion and pulmonary arterial hypertension.
- Nilotinib requires twice daily administration and fasting. It has a black box warning for QT interval prolongation, and has been associated with pancreatitis and hyperglycemia.
- Bosutinib causes significant GI toxicity, particularly diarrhea.
- Ponatinib (Iclusig) is the only TKI that is effective in patients with a specific mutation (T3151+), but it has significant safety concerns, including thrombotic events.

Overall Conclusion

- The choice of drug for CML varies depending on patient comorbidities, provider experience, continued response to initial treatment, prior treatment, and adverse event profiles. Adherence and monitoring of response is essential to treatment success in CML.

References

- DoD P&T Committee minutes: http://www.health.mil/PandT
- Current/future drug classes under review by the DoD P&T Committee:

  http://www.health.mil/PandT (scroll down to DoD P&T Committee Meeting Schedule)
- TRICARE Formulary Search Tool: http://www.health.mil/formulary
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents (including this one) available at: http://www.health.mil/DoDPTResources
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

CML Drug Price Comparison at MTF	
Drug	**MTF Cost/Month (Aug 2015)**
Uniform Formulary	
imatinib (Gleevec)	**$ Most Cost-Effective**
dasatinib (Sprycel)	**$$ Less Cost-Effective**
nilotinib (Tasigna)	**$$ Less Cost-Effective**
bosutinib (Bosulif)	**$$$ Less Cost-Effective**
ponatinib (Iclusig)	**$$$ Less Cost-Effective**
Nonformulary	
None	

Legend:
$ = "Most Cost-Effective" represents Rxs with the lowest cost and/or best clinical efficacy
$$ = "Less Cost-Effective" represents higher cost Rxs with similar clinical efficacy
$$$ = "Less Cost-Effective" represents next higher cost Rxs with similar clinical efficacy
$$$$ = "Least Cost-Effective" represents Rxs with the highest cost with similar clinical efficacy

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